

Y is alkyl or haloalkyl having 1 to about 10 carbon atoms, alkenyl having 2 to about 10 carbon atoms, alkynyl having 2 to about 10 carbon atoms, aryl having 6 to about 14 carbon atoms, N(Q₁)(Q₂), O(Q₁), halo, S(Q₁), or CN;

each q₁ is, independently, from 2 to 10;

each q₂ is, independently, 0 or 1;

m is 0, 1 or 2;

p is from 1 to 10; and

q₃ is from 1 to 10 with the proviso that when p is 0, q₃ is greater than 1.

REMARKS

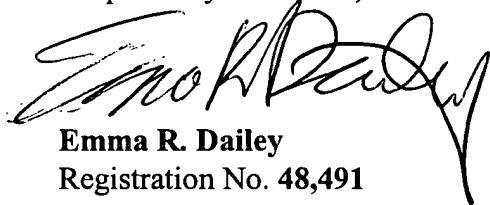
The specification has been amended to reflect the claim of priority. After entry of the above amendment, claims 1-13, 18, and 21-32 will be pending. These claims find support throughout the specification and claims as originally filed.

Applicants have amended the specification to specifically identify sequences with SEQ ID NOS. Applicants have further amended the specification to update SEQ ID NOS and to correct minor typographical errors. No new matter has been added.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

Applicants respectfully request that this amendment be entered and that claims 1-13, 18, and 21-32 be allowed at this time.

Respectfully submitted,



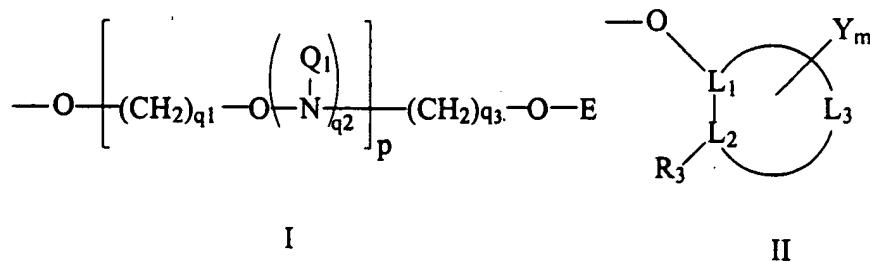
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WHAT IS CLAIMED IS:

1. An oligonucleotide comprising a plurality of nucleotides, wherein:
 - a first portion of said plurality of nucleotides have B-form conformational geometry and are joined together in a continuous sequence, at least two of said nucleotides of said first portion being ribonucleotides or arabinonucleotides; and
 - a further portion of said plurality of nucleotides are ribonucleotide that have A-form conformation geometry and are joined together in at least one continuous sequence.
2. The oligonucleotide of claim 1 wherein each nucleotide of said first portion, independently, is a 2'-SCH₃ ribonucleotide, a 2'-NH₂ ribonucleotide, a 2'-NH(C₁-C₂ alkyl) ribonucleotide, a 2'-N(C₁-C₂ alkyl)₂ ribonucleotide, a 2'-CF₃ ribonucleotide, a 2'=CH₂ ribonucleotide, a 2'=CHF ribonucleotide, a 2'=CF₂ ribonucleotide, a 2'-CH₃ ribonucleotide, a 2'-C₂H₅ ribonucleotide, a 2'-CH=CH₂ ribonucleotide or a 2'-C≡CH ribonucleotide.
3. The oligonucleotide of claim 1 wherein each of said nucleotides of said first portion are joined together in said continuous sequence by phosphate, phosphorothioate, phosphorodithioate or boranophosphate linkages.
4. The oligonucleotide of claim 1 wherein each nucleotide of said further portion, independently, is a 2'-fluoro nucleotide or a nucleotide having a 2'-substituent having the formula I or II:



wherein

E is C_1 - C_{10} alkyl, $N(Q_1)(Q_2)$ or $N=C(Q_1)(Q_2)$;
each Q_1 and Q_2 is, independently, H, C_1 - C_{10} alkyl, dialkylaminoalkyl, a nitrogen protecting group, a tethered or untethered conjugate group, a linker to a solid support, or Q_1 and Q_2 , together, are joined in a nitrogen protecting group or a ring structure that can include at least one additional heteroatom selected from N and O;

R_3 is OX , SX , or $N(X)_2$;
each X is, independently, H, C_1 - C_8 alkyl, C_1 - C_8 haloalkyl, $C(=NH)N(H)Z$, $C(=O)N(H)Z$ or $OC(=O)N(H)Z$;

Z is H or C_1 - C_8 alkyl;
 L_1 , L_2 and L_3 form a ring system having from about 4 to about 7 carbon atoms or having from about 3 to about 6 carbon atoms and 1 or 2 heteroatoms selected from oxygen, nitrogen and sulfur and wherein said ring system is aliphatic, unsaturated aliphatic, aromatic, or saturated or unsaturated heterocyclic;

Y is alkyl or haloalkyl having 1 to about 10 carbon atoms, alkenyl having 2 to about 10 carbon atoms, alkynyl having 2 to about 10 carbon atoms, aryl having 6 to about 14 carbon atoms, $N(Q_1)(Q_2)$, $O(Q_1)$, halo, $S(Q_1)$, or CN ;

each q_1 is, independently, from 2 to 10;

each q_2 is, independently, 0 or 1;

m is 0, 1 or 2;

p is from 1 to 10; and

q_3 is from 1 to 10 with the proviso that when p is 0, q_3 is greater than 1.

5. The oligonucleotide of claim 1 wherein each of said nucleotides of said further portion, independently, is a 2'-F ribonucleotide, a 2'-O-(C₁-C₆ alkyl) ribonucleotide, or a 2'-O-(C₁-C₆ substituted alkyl) ribonucleotide wherein the substitution is C₁-C₆ ether, C₁-C₆ thioether, amino, amino(C₁-C₆ alkyl) or amino(C₁-C₆ alkyl)₂.

6. The oligonucleotide of claim 1 wherein all of said nucleotides of said further portion are joined together in a continuous sequence by 3'-5' phosphodiester, 2'-5' phosphodiester, phosphorothioate, Sp phosphorothioate, Rp phosphorothioate, phosphorodithioate, 3'-deoxy-3'-amino phosphoroamidate, 3'-methylenephosphonate, methylene(methylimino), dimethylhydrazino, amide 3, amide 4 or boranophosphate linkages.

7. The oligonucleotide of claim 1 wherein at least two of said nucleotides of said further portion are joined together in a continuous sequence that is positioned 3' to said continuous sequence of said first portion of said plurality of nucleotides.

8. The oligonucleotide of claim 1 wherein at least two of said nucleotides of said further portion are joined together in a continuous sequence that is positioned 5' to said continuous sequence of said first portion.

9. The oligonucleotide of claim 1 wherein at least two of said nucleotides of said further portion are joined together in a continuous sequence that is positioned 3' to said continuous sequence of said first portion and at least two of said further portion are joined together in a continuous sequence that is positioned 5' to said continuous sequence of said first portion.

10. The oligonucleotide of claim 1 wherein each nucleotide of said first portion, independently, is a 2'-SCH₃ ribonucleotide, a 2'-NH₂ ribonucleotide, a 2'-NH(C₁-C₂ alkyl) ribonucleotide, a 2'-N(C₁-C₂ alkyl)₂ ribonucleotide, a 2'=CH₂ ribonucleotide, a 2'-CH₃,

ribonucleotide, a 2'-C₂H₅ ribonucleotide, a 2'-CH=CH₂ ribonucleotide or a 2'-C≡CH ribonucleotide.

11. The oligonucleotide of claim 1 wherein each nucleotide of said first portion, independently, is a 2'-SCH₃ ribonucleotide, a 2'-NH₂ ribonucleotide a 2'-NH(C₁-C₂ alkyl) ribonucleotide, a 2'-N(C₁-C₂ alkyl)₂ ribonucleotide or a 2'-CH₃ ribonucleotide.

12. The oligonucleotide of claim 1 wherein each nucleotide of said first portion, independently, is a 2'-SCH₃ ribonucleotide, a 2'-NH₂ ribonucleotide or a 2'-CH₃ ribonucleotide.

13. The oligonucleotide of claim 1 wherein each nucleotide of said first portion is a 2'-SCH₃ ribonucleotide.

14. The oligonucleotide of claim 1 wherein each nucleotide of said first portion, independently, is a 2'-CN arabinonucleotide, a 2'-F arabinonucleotide, a 2'-Cl arabinonucleotide, a 2'-Br arabinonucleotide, a 2'-N₃ arabinonucleotide, a 2'-OH arabinonucleotide, a 2'-O-CH₃ arabinonucleotide or a 2'-dehydro-2'-CH₃ arabinonucleotide.

15. The oligonucleotide of claim 1 wherein each nucleotide of said first portion, independently, is a 2'-F arabinonucleotide, a 2'-OH arabinonucleotide or a 2'-O-CH₃ arabinonucleotide.

16. The oligonucleotide of claim 1 wherein each nucleotide of said first portion, independently, is a 2'-F arabinonucleotide or a 2'-OH arabinonucleotide.

17. The oligonucleotide of claim 1 wherein each nucleotide of said first portion is a 2'-F arabinonucleotide.

18. The oligonucleotide of claim 1 wherein each nucleotide of said first portion, independently, is a 2'-SCH₃ ribonucleotide, a 2'-NH₂ ribonucleotide a 2'-NH(C₁-C₂ alkyl) ribonucleotide, a 2'-N(C₁-C₂ alkyl)₂ ribonucleotide, a 2'-CH₃ ribonucleotide, a 2'-CH=CH₂ ribonucleotide or a 2'-C≡CH ribonucleotide; and
each nucleotide of said further portion, independently, is a 2'-F ribonucleotide, a 2'-O-(C₁-C₆ alkyl) ribonucleotide, or a 2'-O-(C₁-C₆ substituted alkyl) ribonucleotide wherein the substitution is C₁-C₆ ether, C₁-C₆ thioether, amino, amino(C₁-C₆ alkyl) or amino(C₁-C₆ alkyl)₂.

19. The oligonucleotide of claim 1 wherein each nucleotide of said first portion, independently, is a 2'-CN arabinonucleotide, a 2'-F arabinonucleotide, a 2'-Cl arabinonucleotide, a 2'-Br arabinonucleotide, a 2'-N₃ arabinonucleotide, a 2'-OH arabinonucleotide, a 2'-O-CH₃ arabinonucleotide or a 2'-dehydro-2'-CH₃ arabinonucleotide; and
each nucleotide of said further portion, independently, is a 2'-F ribonucleotide, a 2'-O-(C₁-C₆ alkyl) ribonucleotide, or a 2'-O-(C₁-C₆ substituted alkyl) ribonucleotide wherein the substitution is C₁-C₆ ether, C₁-C₆ thioether, amino, amino(C₁-C₆ alkyl) or amino(C₁-C₆ alkyl)₂.

20. The oligonucleotide of claim 1 wherein each nucleotide of said first portion, independently, is a 2'-F arabinonucleotide or a 2'-OH arabinonucleotide; and
each nucleotide of said further portion is a 2'-O-(C₁-C₆ substituted alkyl) ribonucleotide wherein the substitution is C₁-C₆ ether, C₁-C₆ thioether, amino, amino(C₁-C₆ alkyl) or amino(C₁-C₆ alkyl)₂.

21. The oligonucleotide of claim 1 wherein said further portion comprises at least two nucleotides joined together in a continuous sequence that is positioned at the 3' terminus end of said oligonucleotide.

22. The oligonucleotide of claim 1 wherein said further portion comprises at least two nucleotides joined together in a continuous sequence that is positioned at the 5' terminus of said oligonucleotide.

23. The oligonucleotide of claim 1 wherein said further portion comprises at least two nucleotides joined together in a continuous sequence that is positioned at the 3' terminus of said oligonucleotide; and
at least two nucleotides joined together in a continuous sequence that is positioned at the 5' terminus of said oligonucleotide.

24. The oligonucleotide of claim 21 wherein said at least two nucleotides joined together comprise nucleotides joined together by a 2'-5' phosphodiester linkage, a 3'-methyleneephosphonate linkage, a Sp phosphorothioate linkage, a methylene(methylimino) linkage, a dimethylhydrazino linkage, a 3'-deoxy-3'-amino phosphoroamidate linkage, an amide 3 linkage or an amide 4 linkage.

25. The oligonucleotide of claim 24 wherein said two nucleotides are joined together by a 2'-5' phosphodiester linkage, a 3'-methyleneephosphonate linkage, a Sp phosphorothioate linkage or a methylene(methylimino) linkage.

26. The oligonucleotide of claim 22 wherein said at least two nucleotides joined together comprise nucleotides joined together by a 2'-5' phosphodiester linkage, a 3'-methyleneephosphonate linkage, a Sp phosphorothioate linkage, a methylene(methylimino) linkage, a dimethylhydrazino linkage, a 3'-deoxy-3'-amino phosphoroamidate linkage, an amide 3 linkage or an amide 4 linkage.

27. The oligonucleotide of claim 26 wherein said two nucleotides are joined together by a 2'-5' phosphodiester linkage, a 3'-methylenephosphonate linkage, a Sp phosphorothioate linkage or a methylene(methylimino) linkage.

28. The oligonucleotide of claim 23 wherein said at least two nucleotides joined together and positioned at said 3' terminus comprise nucleotides joined together by a 2'-5' phosphodiester linkage, a 3'-methylenephosphonate linkage, a Sp phosphorothioate linkage, a methylene(methylimino) linkage, a dimethylhydrazino linkage, a 3'-deoxy-3'-amino phosphoroamidate linkage, an amide 3 linkage or an amide 4 linkage; and
wherein said at least two nucleotides joined together and positioned at said 5' terminus comprise nucleotides joined together by a 2'-5' phosphodiester linkage, a 3'-methylenephosphonate linkage, a Sp phosphorothioate linkage, a methylene(methylimino) linkage, a dimethylhydrazino linkage, a 3'-deoxy-3'-amino phosphoroamidate linkage, an amide 3 linkage or an amide 4 linkage.

29. The oligonucleotide of claim 28 wherein said two nucleotides joined together at said 3' terminus and said two nucleotides joined together at said 5' terminus are, independently, joined together by 2'-5' phosphodiester linkages, 3'-methylenephosphonate linkages, Sp phosphorothioate linkages or methylene(methylimino) linkages.

30. The oligonucleotide of claim 21 wherein at least one of said two nucleotides joined together is a 2'-alkylamino substituted nucleotide.

31. The oligonucleotide of claim 22 wherein at least one of said two nucleotides joined together is a 2'-alkylamino substituted nucleotide.

32. The oligonucleotide of claim 23 wherein at least one of said two nucleotides joined together at said 3' terminus is a 2'-alkylamino substituted nucleotide, and
wherein at least one of said two nucleotides joined together at said 5' terminus is a 2'-alkylamino substituted nucleotide.

33. ~~An oligonucleotide comprising a plurality of linked nucleotides, wherein:
at least one of said nucleotides has a C3' endo type pucker; and
at least two of said plurality of nucleotides are joined together in a continuous sequence
and have a C2' endo type pucker or an O4' endo type pucker, provided that said nucleotides are
not 2'-deoxy-erythro-pentofuranosyl nucleotides.~~

34. The oligonucleotide of claim 33 wherein said nucleotides having said C3' endo type pucker are joined together in a continuous sequence that is positioned 3' to said continuous sequence of nucleotides having said C2' endo type pucker or O4' endo type pucker.

35. The oligonucleotide of claim 33 wherein said nucleotides having said C3' endo type pucker are joined together in a continuous sequence that is positioned 5' to said continuous sequence of nucleotides having said C2' endo type pucker or O4' endo type pucker.

36. The oligonucleotide of claim 33 wherein at least two of said nucleotides having said C3' endo type pucker are joined together in a continuous sequence that is positioned 3' to said continuous sequence of said nucleotides having said C2' endo type pucker or O4' endo type pucker; and

at least two of said nucleotides having said C3' endo type pucker are joined together in a continuous sequence that is positioned 5' to said continuous sequence of said nucleotides having said C2' endo type pucker or O4' endo type pucker.

ABSTRACT OF THE DISCLOSURE

[0291] Modified oligonucleotides containing both A-form conformation geometry and B-form conformation geometry nucleotides are disclosed. The B-form geometry allows the oligonucleotide to serve as substrates for RNase H when bound to a target nucleic acid strand. The A-form geometry imparts properties to the oligonucleotide that modulate binding affinity and nuclease resistance. By utilizing C2' endo sugars or O4' endo sugars, the B-form characteristics are imparted to a portion of the oligonucleotide. The A-form characteristics are imparted via use of either 2'-O-modified nucleotides that have 3' endo geometries or use of end caps having particular nuclease stability or by use of both of these in conjunction with each other.